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Increased wheezing risk with diesel exposure among children of younger mothers

To the Editor:

Lower respiratory tract illnesses (LRIs) are the largest cause of mortality among young children worldwide [1], and are associated with altered lung function, immune system development and respiratory disease in adulthood [2, 3]. Several studies have demonstrated associations between wheezing LRIs in early life and exposure to diesel traffic related air pollutants (D-TRAP) [1, 4, 5]. We, along with others, have previously demonstrated that younger maternal age at birth is also a risk factor for wheezing LRIs in the first year of life [6, 7]. Why children of younger mothers are more susceptible is unknown, but both altered responses to environmental challenges in their offspring due to maternal immaturity [6] and increased socioeconomic and environmental risks have been proposed as causes [8].

We postulated that children of younger mothers are more susceptible to environmental exposures than children of older mothers. To test this hypothesis, we used data from the Tucson Children's Respiratory Study, a longitudinal birth cohort designed to investigate risk factors for LRIs in early childhood and chronic lung disorders later in life [9, 10]. Through age 3 years, LRIs were diagnosed by study physicians who documented wheeze [10]. Parents were asked if their child had active wheeze during the past year at 6 years. Four wheezing phenotypes were defined: never, transient-early (only to age 3 years), late-onset (by age 6 but not by age 3 years), and persistent (by age 3 and 6 years) [11]. The study was approved by the University of Arizona Human Subjects Committee. Informed consent was obtained from a parent of a participating child.

We estimated D-TRAP exposure for each enrolment address using CAL3QHC, a Gaussian line-source dispersion model [12], that estimates traffic pollutant concentrations as a function of distance to roadway, traffic volume, wind speed and direction, atmospheric stability class, and vehicle emissions. We only used highways in our analysis, as they represent the primary source of diesel exhaust in Tucson, AZ, USA. Roadway and meteorological data corresponding to each participant's season of birth were obtained from the Arizona Department of Transportation and the National Weather Service. Emissions factors were computed with the United States Environmental Protection Agency's MOBILE 6.2 model for PM_{2.5} by diesel vehicle class.

We geocoded each participant's enrolment address using ArcGIS 10 (ESRI, Redlands, CA, USA), and obtained D-TRAP exposure for these coordinates with CAL3QHC. D-TRAP estimates represent seasonal exposures to a mixture of air pollutants from proximity to highway diesel traffic emissions independent of other diesel exhaust sources, and are interpreted as a unitless index.

Because our outcome was a count variable (*i.e.* number of wheezing LRIs) and 62% had no wheezing LRI (mean 0.62, variance 1.00), we used a negative binomial regression to account for over-dispersion in assessing the relationship between D-TRAP exposure and wheezing LRI events. Multinomial regression was used to assess associations with wheezing phenotypes. Interaction terms were included to assess effect modification. We examined pairwise associations between D-TRAP exposure, maternal age, and wheezing LRIs, with potential confounders (*i.e.* sex, ethnicity, maternal education, household cooling methods, older children in the home, marital status and census tract socioeconomic status, among others). We used the robust cluster estimator of variance to account for potential clustering by census tract. To assess multi-collinearity, we calculated the variance inflation factor for the final adjusted models. STATA 13.0 (StataCorp, College Station, TX, USA) was used for all analyses.

Of the original 1246 children enrolled, 825 had enrolment addresses from which D-TRAP exposure could be estimated and were followed by study physicians for the first 3 years of life: 23.3% had one wheezing LRI; 8.5% had two; and 6.1% had three to five. There was no difference in the distribution of D-TRAP exposure between children included in the analyses and those with incomplete follow-up ($p=0.32$). Included participants were more likely to be White or Hispanic, to have older mothers with >12 years of schooling, and to live in a house with evaporative cooling.

Each log increase of D-TRAP exposure was associated with an increased incidence rate ratio for wheezing LRIs (table 1). Children of mothers <21 or 21–25 years old had a significantly higher incidence rate ratio per log increase of D-TRAP exposure (table 1). D-TRAP exposure was associated with transient wheezing among children with mothers <21 years old (OR 2.55, 95% CI 1.04–6.24) and 21–25 years old (OR 1.75, 95% CI 1.17–2.60), but not among children with older mothers (OR 0.98, 95% CI 0.77–1.26 for 26–30 years old and OR 1.07, 95% CI 0.79–1.47 for >30 years old). Late-onset and persistent wheezing phenotypes were not associated with D-TRAP exposure.

Increased D-TRAP exposure at enrolment and younger maternal age were both associated with Hispanic ethnicity, less maternal education, or living in a census tract with low socioeconomic status. Younger maternal age was also associated with marital status, fewer older children in the home, and household use of evaporative cooling. However, results remained consistent after adjustment for these potential confounders (table 1).

To our knowledge, this is the first study demonstrating that younger maternal age modifies the effect of air pollution on children’s respiratory outcomes. Factors directly or indirectly related to maternal age such as biological factors associated with lung growth may make their infants more susceptible to wheeze with increased D-TRAP exposure. Younger mothers are at increased risk of preterm delivery, with lower birth weight or small for gestational age babies, independent of socioeconomic status [13], all of which are risk factors for reduced lung function later in life, although that did not account for the relationships reported here.

Prenatal exposures to particulate matter are more strongly associated with recurrent wheezing LRIs than childhood exposures [4]. Furthermore, younger maternal age modifies the association of prenatal carbon monoxide exposure and low birth weight [14]. These studies suggest that younger mothers may be more susceptible to air pollution exposures, perhaps due to their own physical immaturity while the child is *in utero*.

Maternal age may be a proxy for an unknown social or environmental factor not considered resulting in residual confounding, such as lack of prenatal care [15]. Differential exposure misclassification by maternal age could also have affected our results. Younger mothers are more likely than older mothers to work or attend school near their homes, and thus may be more accurately characterised by air pollution levels at their home address [14].

The strength of our study is that all LRIs were assessed prospectively by study physicians using predefined criteria in a non-selected cohort. However, recruitment through a health maintenance organisation probably

TABLE 1 Incidence rate ratio (IRR) for wheezing lower respiratory tract illnesses in the first 3 years of life by 1) diesel traffic related air pollutant (D-TRAP) exposure, 2) maternal age, and 3) D-TRAP exposure by maternal age category

Exposure	Subjects n	Crude			Adjusted [#]		
		IRR	95% CI	p-value	IRR	95% CI	p-value
Model 1: D-TRAP[¶]	822	1.13	1.03–1.23	0.009	1.07	0.98–1.17	0.13
Model 2: maternal age							
<21 years	42	1.01	0.66–1.54	0.96	1.06	0.70–1.63	0.77
21–25 years	238	1.33	1.01–1.76	0.04	1.35	1.04–1.76	0.02
26–30 years	316	1.14	0.88–1.47	0.34	1.20	0.93–1.56	0.17
>30 years	229	Reference			Reference		
Model 3: D-TRAP by maternal age[¶]							
<21 years	42	1.35	1.05–1.74	0.02	1.31	1.02–1.67	0.03
21–25 years	238	1.33	1.14–1.57	<0.001	1.25	1.07–1.45	0.005
26–30 years	316	0.96	0.82–1.13	0.63	0.94	0.81–1.11	0.47
>30 years	229	0.97	0.80–1.17	0.75	0.92	0.75–1.12	0.42

Results are from negative binomial regression models, and statistically significant associations are indicated in boldface. An interaction term was included in model 3 with D-TRAP exposure and maternal age, evaluated with the Wald test (chi-squared 16.94, degrees of freedom 3, $p=0.0007$). [#]: adjusted for child ethnicity (variance inflation factor (VIF) 1.19), older children in the household (VIF 1.10), household cooling methods (VIF 1.03) and census tract socioeconomic status (VIF 1.23). VIF was 1.11 and 1.13 for D-TRAP and maternal age, respectively. [¶]: IRR per log increase in D-TRAP exposure.

under-represented children of low socioeconomic status [9]. Unfortunately, air pollution measurements were not taken at participants' homes, and adequate existing data corresponding to that time period (1980–1987) are unavailable. By modelling highway truck traffic emissions, the primary source of diesel exhaust in Tucson, we have probably identified the children chronically exposed to higher levels of D-TRAP. Greater exposure specificity would presumably lead to stronger associations than we have reported.

In summary, the association of wheezing LRIs with D-TRAP exposure was stronger in children of younger mothers, who were also more likely to have transient-early wheezing with increasing D-TRAP exposure. Biological and social risk factors associated with younger maternal age may explain these findings. Given that younger mothers are more likely to live in areas of increased diesel traffic exposure, targeting exposure prevention strategies specifically for children of younger mothers may be warranted.



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Association of wheeze with diesel pollution exposure is stronger in children of younger mothers
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